Katsunori Kagohashi[1], Kunihiko Miyazaki[2], Toshihiro Shiozawa[3], Hiroaki Satoh[1]

[1]Division of Respiratory Medicine, Mito Medical Center, University of Tsukuba, Mito-city, Japan
[2]Division of Respiratory Medicine, Ryugasaki Saiseikai Hospital, Ryugasaki-city, Japan
[3]Division of Respiratory Meidicine, Facaulty of Medicine, University of Tsukuba

Pseudoprogression during successful rechallenge of immune checkpoint inhibitor in a NSCLC patient

Abstract

Rechallenge of immune checkpoint inhibitors (ICPIs) is one of the attractive but unestablished treatment for recurrent non-small cell lung cancer (NSCLC) patients who have been treated with several lines of systemic chemotherapy. In some NSCLC patients, the effects of ICPI rechallenge therapy have become apparent. In ICPI treatment, although very rare, a phenomenon called pseudoprogression is known. We report the first case of pseudoprogression during successful rechallenge of ICPI in a NSCLC patient. Although not fully clarified, factors related to the onset of pseudoprogression and good response to ICPI rechallenge are being investigated. Our case showed that pseudoprogression could be developed even in patients with ICPI rechallenge therapy.

Key words: rechallenge, immune checkpoint inhibitor, pseudoprogression, non-small cell lung cancer

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Introduction

With the development of immune checkpoint inhibitors (ICPIs), treatment of advanced non-small cell lung cancer (NSCLC) has dramatically changed [1]. At present, ICPIs are available in first-line NSCLC treatment with or without chemotherapy, and they can be administered even after the second or later line treatments. This clinical situation may provide opportunities for ICPI rechallenge therapy in later lines after the recurrence on post-ICPI chemotherapy or driver gene targeted therapies. In some NSCLC patients, the effects of ICPI rechallenge therapy have become apparent [2–7]. We have encountered a NSCLC patient who showed pseudoprogression [8–11], which is very rare phenomenon in this therapy, during successful ICPI rechallenge treatment. To our best knowledge, this is the first case with such a very rare phenomenon during successful rechallenge of ICPI therapy.

Case report

A 68-year-old man presented with abnormal opacity on chest radiograph detected incidentally. The patient underwent a whole-body computed tomography (CT) , which revealed a nodule in the middle lobe and multiple small nodules in both lung. He was pathologically diagnosed to have adenocarcinoma of the lung. On immunohistochemical staining for programmed death-ligand 1 (PD-L1) using the PD-L1 IHC 22C3 (pharmDX Dako, Merck & Co, NJ, USA), 75% of the tumor cells were positively stained. No driver gene was found. He received first-line chemotherapy with carboplatin and pemetrexed. As therapeutic effect was evaluated as stable disease (SD), he received additional 12 courses of maintenance therapy with pemetrexed. Despite of the treatment, regrowth in left mediastinal lymph nodes was detected in CT scan. Therefore, the patient received an immune checkpoint inhibitor (ICPI), pembrolizumab as

Address for correspondence: Hiroaki Satoh, Division of Respiratory Medicine, Mito Medical Center, University of Tsukuba, Mito-city, Japan; e-mail: hirosato@md.tsukuba.ac.jp

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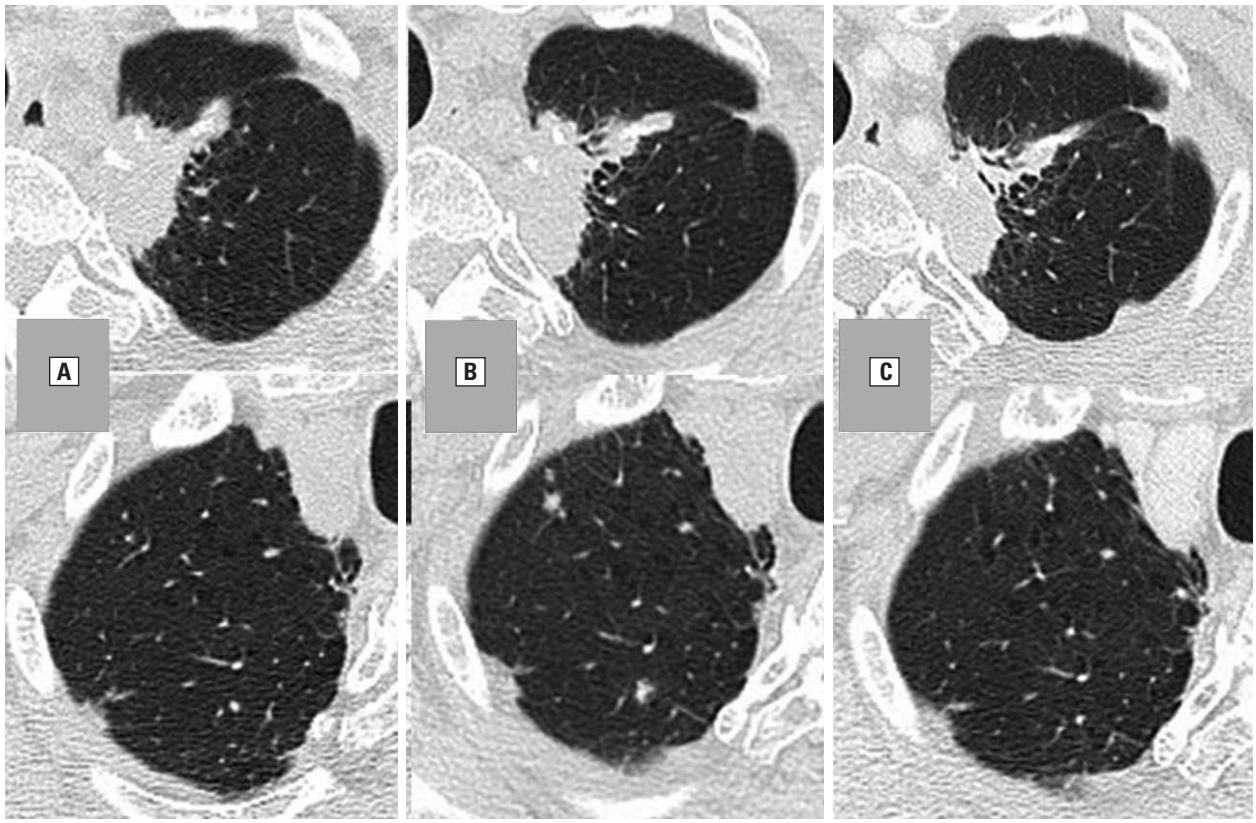

Figure 1. Regrowth of the left mediastinal lesion was found in chest CT scan 10 months after the initiation of the fourth-line chemotherapy (**A**). Enlargement of the left mediastinal lesion and pulmonary metastases were found in chest CT scan taken at 4 weeks after the initiation of the rechallenge therapy (**B**). The left mediastinal lesion was shrunk and pulmonary metastases decreased in size or disappeared in chest CT scan taken at 12 weeks after the initiation of the rechallenge therapy (**C**)

second-line therapy, considering high PD-L1 results. Seven months after the initiation of pembrolizumab, recurrence on left mediastinal lesion was found again in CT scan. Then the patient received the third- and fourth-line chemotherapy with docetaxel and ramucirumab, and carboplatin, pemetrexed and bevacizumab. Response of third- and fourth-line therapy was evaluated as SD. Ten months after the initiation of the fourth-line chemotherapy, regrowth of left mediastinal lesion and development of multiple small lung metastases in both lungs (Figure 1A) were observed. The development of spinal metastases was also found in CT scan. After fully explaining and confirming the patient's consent, ICPI rechallenge using nivolumab was initiated. Simultaneously, irradiation to the vertebral metastatic lesion was performed. In chest CT scan taken at 4 weeks after the initiation of the rechallenge therapy, the left mediastinal lesion was enlarged and the increase in size of pulmonary metastases were found (Figure 1B). However, the patient's general condition did not deteriorate and his willingness to treat was strong, so treatment was continued. In chest CT scan taken at 12 weeks after the initiation of the rechallenge therapy, the left mediastinal lesion was shrunk and pulmonary metastases decreased in size or disappeared (Figure 1C). Response was evaluated as PR. Thereafter, nivolumab was continued for 3 months and he was well with no recurrence. In chemotherapies, the patient developed G3 neutropenia, but had no thrombocytopenia. There was no development of febrile neutropenia. In ICPI therapies, the patient had no immune-related adverse event. The consecutive lines of treatment in the man with progression-free survival indication is shown in Figure 2.

Discussion

At present, according to some guidelines, in patients with high PD-L1 expression (> 50%), pembrolizumab in the first-line setting is recommended (ESMO and NCCN) [12, 13]. However, first-line treatment in our patient started 3 months before pembrolizumab became available in our country. Therefore, the first-line treatment was chemotherapy instead of pembrolizumab.

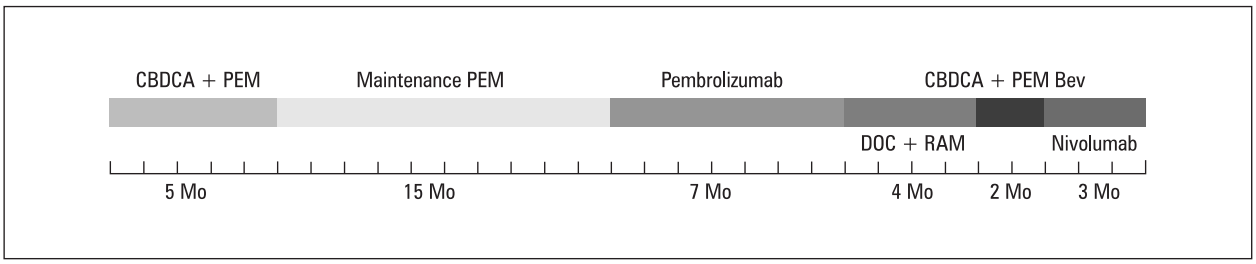

Figure 2. The consecutive lines of treatment in a patient with progression-free survival indication

Pseudoprogression has been defined as an initial disease progression followed by a subsequent response [8]. This phenomenon is rare, and it is reported in 2% to 8% of patients with advanced NSCLC treated with anti-PD-1/PD-L1 agents [9–11]. Pseudoprogression was only observed in patients who received ICPC therapy for the first time. There have been no subjects who developed pseudoprogression in ICPI rechallenge therapy because ICPI rechallenge itself was not an established treatment. To our best knowledge, this is the first case report describing a pseudoprogression developed in successful rechallenge of ICPI therapy for a recurrent NSCLC patient. Clinicopathological factors that predict the development of pseudoprogression, including clinical factors and laboratory findings (e.g., size of tumors, peripheral blood counts, circulating tumor DNA, cytokine levels) have been investigated [11, 14]. However, these potential biomarkers have been inconsistent, probably due to small sample sizes, different tumor types, and heterogeneous definitions of these atypical responses [14]. Investigating the presence and activity of immune cells in the tumor area at the time of tumor growth by tumor biopsy might help assess tumor immunity, nevertheless, this has not yet been proven as a validated biomarker [14]. Considering the frequency of pseudoprogression, it is not practical to perform a tumor biopsy when the tumor grows. Lee *et al.* [15] showed that circulating tumor DNA decreased in the presence of pseudoprogression, but this method has not reached the level of clinical application. Therefore, unfortunately, no reliable assessment has been reported to date to help clinicians decide between a potential pseudoprogression or a real progression [11, 14].

Although it remains unknown in which patients ICPI rechallenge might be effective, on the other hand, previous studies have suggested the predictive factors of the efficacy of the therapy [2–7]. Some of them were as follows: 1) high tumor PD-L1 expression [5], 2) good response to the first ICPI therapy [2, 6, 7], 3) radiation therapy before ICPI rechallenge [4, 6], 4) short duration between the initial ICPI therapy and the rechallenge [3, 6], 5) good response to prior chemotherapy [3], 6) presence of immune-related adverse events in initial ICPI therapy [6], and 7) prior therapy including vascular endothelial growth factor inhibitor [3]. Some of the factors were relevant to our patient. Among them, 'good response to the first ICPI therapy' and 'short duration between the initial ICPI and the rechallenge' was apparently inconsistent. As for predictive factors of the efficacy of rechallenge therapy, there are contradictions and confusions like this. In a large study using national data base, Levra *et al.* [2] suggested that the outcome after retreatment with ICPI following a first course of ICPI was significantly better in patients with a longer duration of initial ICPI treatment. Identification of which patients most benefit from rechallenge with ICPIs and which patients do not, will be one of the most important question to address in future studies.

We reported a pseudoprogression in successful rechallenge ICPI therapy for a NSCLC patient. As shown in our case, pseudoprogression could be developed even in patients with ICPI rechallenge. When several therapies are exhausted, indications for ICPI rechallenge may be considered. The clinical experience in our patient might help in that time.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Mito Medical Center, University of Tsukuba-Mito Kyodo General Hospital (Mito, Japan; approval no. 16-39). Written informed consent to report was obtained from the patient.

Conflict of interest

None declared.

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